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REMARKS

Claims 16, 26 and 28 have been amended. No new matter is introduced and no new issue is raised by the claim amendments.

Claims 16 to 31 were rejected under 35 U.S.C. 112 second paragraph as indefinite. It is submitted this rejection is improper and should be withdrawn.

While Applicants believe that the claims as originally presented were sufficiently definite, Applicants have amended 16, 26 and 28 for formal purposes only.

It appears from the Office Action that the Examiner is having difficulty in understanding the phraseology employed in certain claims. Claim 16, 26 and 28 as amended when referring to the active ingredient is worded so as to include candesartan alone as the active ingredient, a pharmaceutically suitable ester of candesartan alone as the active ingredient or a pharmaceutically suitable salt of candesartan alone as an active ingredient. The phrase also includes combinations of candesartan and one or more of its esters or salts. This is the reason for the use of the expression "at least one of".

It is submitted this phraseology is not indefinite and is similar in form to Markush language. However, Applicants wish to include as the first active ingredient either the candesartan alone, the ester alone, or the salt alone, or combinations of two or more of the candesartan, the ester or salt. Thus, there is no indefiniteness in the language of the claim. It is again submitted that the decision of *Ex Parte Wu* has no bearing on, and is not relevant to, the language employed in the presently pending claims.

Claims 16, 17 and 20 and 22 have been rejected under 35 U.S.C. 102(e) as anticipated by Frangin. It is submitted this rejection is improper and should be withdrawn.

For a reference to anticipate a claimed invention, that single reference must show each feature recited in the claim and each of those features must be arranged as in the claim (identity). Further, the reference must include an enabling disclosure so that one of ordinary skill in the art can practice the invention (enablement).

It is submitted that Frangin is not an anticipatory reference.

The present invention addresses the problem of providing a form of administration for candesartan and/or esters or salts to overcome the drawbacks of previously oral or intravenous forms of administration. These drawbacks included low bioavailability, hepatic metabolization with toxic byproducts or frequent repeat of application.

Frangin teaches the use of benzofuran derivatives, such as amiodarone, for the prevention of mortality following a myocardial infarction. Frangin's examples show tablets or injectable solutions with amiodarone or dronedarone. Clinical studies for amiodarone tablets reveal the reduction of mortality. Benzofuran derivatives with antiarrhythmic activity may be combined with another cardioactive agent e.g. ACE-inhibitors, diuretics, angiotensin II inhibitor (like candesartan). Frangin does not teach a transdermal therapeutic system containing candesartan or an ester or salt thereof. A passing mention of a transdermal delivery system does not meet the identity or enablement requirement.

It is submitted that Frangin does not anticipate the now claimed subject matter because it does not identify the presently claimed invention and it does not enable one of ordinary skill in the art to make the invention.

The original patent for candesartan, U.S. Patent 5,196,444, included a discussion of the various methods of administration of that substance. However, there is no mention in the basic '444 patent of using a transdermal drug delivery system to administer candesartan. As indicated

above, Frangin includes only a passing mention of a transdermal delivery system. It is submitted that this passing mention does meet the identity or enable requirement for a reference to be an anticipatory one. Further, Jalonen teaches that only certain compounds are suitable for transdermal delivery. Thus, the state of the art at the time was such that while the basic technology for transdermal delivery systems may have been known, it was also known that such systems could not be applied to all substances.

The data presented in Frangin starting on column 7 relates to tablets, gelatin capsules, and formulations for parenteral administration. No formulation is presented for use as a transdermal patch. The clinical study reported starting at column 9 and continuing on to column 11 of Frangin relates to the use of tablets. Thus, the reference fails both to sufficiently identify the invention and fails to provide any enablement with respect to the transdermal delivery system. Accordingly, Frangin cannot be an anticipatory reference especially in view of Jalonen which establishes that in the art, it was known that not all pharmaceutically active compounds are suitable for transdermal administration due to many different pharmokinetic and pharmacological reasons. See Jalonen in column 2, lines 13 to 29.

Claims 16, 17 and 19 to 22 have been rejected under 35 U.S.C. 103(a) as unpatentable over Poss in view of Frangin. It is submitted this rejection is improper and should be withdrawn.

Poss teaches quinoline derivatives useful as angiotensin II inhibitors. Candesartan is not a quinoline derivative. Poss only suggests certain quinoline derivatives (column 7, line 49-58; column 8, line 19-23) to be administered by oral, intranasal, transdermal, parenteral,... means. No examples for transdermal patches with angiotensin II inhibitors are reported. Nor does the reference suggest that any of the preparations of the examples are useful for a transdermal

administration. Thus, it is not possible to obtain a working transdermal patch with candesartan as active ingredient by way of the combination of Poss and Frangin.

Applicant incorporates the previous comments with respect to the Frangin reference set forth above.

Claims 23 to 31 have been rejected under 35 U.S.C. 103(a) as unpatentable over Poss and Frangin in view of Jalonen. It is submitted this rejection is improper and should be withdrawn.

Jalonen teaches substituted imidazole derivatives which are a_2 adrenoceptor antagonists for transdermal administration. Matrix- and reservoir transdermal delivery systems are disclosed.

Candesartan (2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylic acid) is much more complex than Jalonen's imidazole derivatives. It is not obvious that candesartan is suitable for transdermal administration. Neither Frangin, Poss nor Jalonen show that candesartan is suitable for transdermal application.

Jalonen acknowledges that not all therapeutically active substances are suitable for transdermal administration at column 2, starting at lines 13 to 29 which reads as follows:

> Only a minor part of commercially available therapeutically active substances is suitable for transdermal administration due to many different pharmacokinetic and pharmacological reasons. One of the most limiting factors is, however, the physiocochemical properties of the therapeutically active substance itself. For a compound to be able to penetrate the skin it must have both lipophilic (fat soluble)and hydrophilic (water soluble) properties in a suitable proportion. Such a suitable ratio between the lipophilic and hydrophilic properties is not very common for drug substances. The ability of a drug to penetrate through the skin can be predicted by its partition coefficient P in octanol/water. It is known that compounds having an optimal partition coefficient penetrate the skin better than compounds with either higher or lower partition coefficients. This optimal partition coefficient value is different for different kinds of compounds.

Accordingly, any broad conclusion of obviousness is not warranted and the art specifically teaches away from such a broad conclusion.

It is submitted that the combination of references is improper. It is clear that the rejections are based on hindsight reconstruction of one more of the references wherein a reference has been edited or only a minor part of the reference has been considered. As acknowledged by Jalonen, not all therapeutically active substances are suitable for transdermal administration. Therefore, a passing mention, such as in Frangin, of transdermal administration without support by examples showing an operative embodiment cannot be relied upon either for purposes of anticipation or for purposes of obviousness. The mere fact that there is mention in the art of one or more features of the invention does not justify a combination of the references. See *In re Grabiak* 226 U.S.P.Q. 870 (Fed. Cir. 1985).

On page 7 of the Official Action, the Examiner responds to the previously submitted arguments. It is respectfully submitted that the Examiner has not addressed the previously submitted arguments. The Examiner does not address the identity or enablement requirements and does not point out specifically were in Frangin the invention as now claimed is specifically identified or where that invention is enabled. Rather, the Examiner basically repeats portions of the prior rejection and concludes "such language does suggest transdermal system containing candesartan". However, the Examiner never states that Frangin discloses such a system. As set forth above, the standard for a reference to be an anticipatory one, rather than one which is cited for obviousness, is quite different. Accordingly, the Examiner has not established on the record that Frangin is an anticipatory reference.

The Examiner then continues that she has established a prima facie case of obviousness and therefore need not comply with requirements of 37 C.F.R. 1.104(d)(2). It is submitted the

Examiner has failed to establish a prima facie case of obviousness. Furthermore, Applicants request, which is hereby repeated, was in connection with the Examiner's underlying assumption regarding the enablement issue. None of the cases cited by the Examiner pertain to where the applicant has called upon the Examiner to comply with the provisions of 37 C.F.R. 1.104(d)(2) or its predecessor regulation.

Next, the Examiner states that Poss is not limited to his examples but is relied upon for the teaching within the four walls of the patent. However, the Examiner is going beyond the four walls of the Poss because candesartan is not a quinoline. Thus, the Examiner is going beyond disclosure of the patent and any reference to transdermal administration refers to the compounds which are the subject of the Poss patent which are, as stated above, quinolines.

Next, the Examiner appears to argue that because Jalonen does not specifically exclude certain compounds, that means Jalonen suggests that the non-excluded compounds can be used. Such reasoning is not proper. A reference must disclose or suggest. The standard is not that a reference fails to exclude. If "fail to exclude" were the standard, all subject matter which was not specifically excluded or not mentioned would, in the Examiner's view, be suggested and enabled. Failure to exclude is the antithesis of disclosure and conflicts with the underlying policy and constitutional purpose of the patent laws.

The Examiner acknowledges that obviousness can only be established by combining or modifying the teachings of the prior art and that motivation to do is required for the combination. However, in the instant matter, the Examiner's efforts to establish motivation are lacking. The mere fact that it is desired to obtain a beneficial result does not in and of itself establish motivation. What is needed to establish motivation is something in the prior art or in the general body of knowledge that specifically points to the particular modification or combination as one or

one of many, which has a reasonable expectation of success to achieve that beneficial result. That standard is not present in the rejection. In fact, the Jalonen reference, which was cited by the Examiner - not the Applicants, teaches away the conclusion of obviousness made by the Examiner.

In view of the foregoing, reconsideration and allowance of the application with claims 16 to 31 are earnestly solicited.

The Examiner has indicated that the German language DE 4341444 was not entered into the record because specific comments were not provided as to its relevance. This document was cited in a Search Report of the German Patent Office. Apparently, it was cited to define the general state of the art and disclosed a transdermal patch comprising a drug reservoir layer softening at body temperature. The reference does not mention candesartan. It is not believed this document is anymore relevant than that cited and applied on the record by the Examiner.

The Examiner is invited after reviewing the foregoing to phone applicant's undersigned attorney to advise of the status of the application so as to minimize any needless expense or delay.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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AMENDMENTS TO THE CLAIMS SHOWING CHANGES

IN THE CLAIMS:

16. (Twice Amended) A transdermal therapeutic system with a content of a first active ingredient, said first active ingredient comprising at least one of candesartan, [and one of] its pharmaceutically suitable esters or salts.

26. (Twice Amended) The transdermal therapeutic system of claim 23 wherein the system is a matrix system comprising:

an impermeable covering layer;

at least one active ingredient-containing contact adhesive matrix layer or at least one ingredient-containing matrix layer coated with a contact adhesive;

a detachable protective layer; and

an active ingredient comprising at least one of candesartan, [and one of] its pharmaceutically acceptable esters or salts.

28. (Twice Amended) The transdermal therapeutic system of claim 23 wherein the membrane system comprises:

an impermeable covering layer;

an active ingredient-containing reservoir or an active ingredient-containing reservoir layer;

a microporous or semipermeable membrane;

an optional contact adhesive layer; and

an active ingredient comprising at least one of candesartan, [and one of] its pharmaceutically acceptable esters or salts.